REMARKS

Claims 1-5 and 7-45 remain pending with new claims 46 and 47 introduced by the above amendment. Claims 1 and 13-14 have been amended to be consistent with the invention as examined (discussed below). Claim 1 has also been amended to include partial and full retro-inverso embodiments which are supported at least by claims 13 and 14 as originally presented as well as by page 13, lines 22-25, and page 17, lines 10-12. Claim 1 has also been amended to include the subject matter of claim 6, which has been canceled.

Claims 2 and 9 have been amended to utilize alternative language without altering the scope of the claims. Claims 4 and 5 have been amended to conform them to the language of amended claim 1. Claim 4 has also been amended to correct an informality.

Claim 7 has been amended to revise its dependency due to the cancellation of claim 6. Claim 10 has been revised to include a sequence identifier and to be in independent form due to the cancellation of claim 6.

Previously independent claims 11, 15, 20, 26, 29, 30, 37 and 44 have been amended to be dependent from claim 1. Support for these amendments is provided by these claims as originally filed.

New claims 46 and 47 are directed to subject matter in claims 1 and 4 as previously presented.

The amendments are made for reasons related to the Restriction Requirement as previously presented by the Office and the elected and examined invention. The amendments are not in acquiescence to any rejection of record. Applicants reserve the right to pursue the subject matter no longer within the scope of the amended claims in a divisional or other continuing application without prejudice.

No new matter has been introduced, and entry of the amendments is respectfully requested.

Restriction Requirement/Elected Invention

Applicants confirm the election with traverse of SEQ ID NO:51 (NVRF) followed by "VF". Applicants also wish to express their appreciation for the Examiner's extension of the

search and examination to include SEQ ID NO:54 (DVRF). As provided by the above amendments, the subject matter of SEQ ID NO:54 has been moved from claims 1 and 4 to new claims 46 and 47 to facilitate their consideration. Specifically, new claim 46 is directed to a

> "peptide comprising the sequence R_1-D-V-R-F-R_2, or partial or full retro-inverso sequences thereof, wherein R_1 is a hydrogen or a peptide of 1 to 6 amino acids, an acyl or an aryl group; and R_2 is a peptide of 2 or 3 amino acids, a hydroxide or an amide."

As such, claim 46 is specifically directed to embodiments of the invention relating to SEQ ID NO:54, with claim 47 directed to a peptide that is specified further.

Applicants respectfully submit that new claims 46 and 47 are properly part of the elected and examined invention and should be examined with elected claims 1-10, 13 and 14.

Applicants further wish to express their appreciation for the Examiner's recognition of the standards at MPEP 806.05(c) for restriction between inventions that are related as combination and subcombination. In particular, Applicants appreciate the recognition that such related inventions can only be distinct if the combination does not require the particulars of the subcombination for patentability.

Withdrawn claims 11, 12, and 15-19 have been amended to be dependent from claim 1. As such, they are all directed to combinations comprising the subcombination of the peptides of claim 1, which is required for the patentability of claims 11, 12, and 15-19. Accordingly, no restriction between elected claims 1-10, 13 and 14 and amended claims 11, 12, and 15-19 is proper.

In light of these amendments, Applicants respectfully submit that the withdrawal of claims 11, 12, and 15-19 from consideration may be reconsidered and withdrawn so that claims 11, 12, and 15-19 are examined with elected claims 1-10, 13 and 14.

Claims 20-45 have been amended to be directed to methods comprising the use of a peptide according to claim 1 (claims 20-29 and 31-45) or claim 2 (claim 30). As such, they have all the limitations of elected claims 1 and 2 and are subject to rejoinder as set forth at MPEP

821.04. Applicants respectfully request that Examiner Haddad acknowledge the applicability of the rejoinder rules in the next Office communication.

Further, Applicants wish to express their understanding that the search and examination of elected claims 1-10, 13 and 14 has been extended beyond SEQ ID NO:51 (NVRF) followed by "VF" and SEQ ID NO:54 (DVRF) as evinced by the application of references disclosing the sequences "QVRI", "DLRL" and "SLRF" on pages 6-9 of the Office Action mailed 21 May 2004. Based upon the consideration of these additional sequences, which are within the scope of claim 1 as previously presented, Applicants understand the Office Action to reflect the search and examination of claims at least with respect to peptides comprising the sequence R1-X1-X2-X3-X4-R2 wherein

> -- X1 is selected from the group consisting of N, Q, D and S (because N is found in SEQ ID NO:51 as elected, Q is found in the sequence discussed in paragraph 15 of the Office Action, D is found in the sequence discussed in paragraphs 16 and 17 of the Office Action, and S is found in the sequence discussed in paragraph 18 of the Office Action);
>
> --X2 is V (because V is found in both SEQ ID NOs:51 and 54 as well as the sequences discussed in paragraphs 15 and 17 of the Office Action);
>
> --X3 is R (because R is found in both SEQ ID NOs:51 and 54 as elected as well as in all four sequences discussed on pages 6-8 of the Office Action); and
>
> --X4 is selected from the group consisting of L and F (because L is discussed in the sequence discussed in paragraph 16 of the Office Action; and F is found in both SEQ ID NOs:51 and 54 as elected as well as the sequences discussed in paragraphs 17 and 18 of the Office Action).

In light of the search and examination of additional sequences as evinced by pages 6-9 of the Office Action, claim 1 has been amended to be better tailored to the expanded

examination as reflected in the Office Action. Specifically, positions X2 and X3 have now been specified as V and R, respectively. Additionally, position X4 is specified as being either L or F. None of these amendments introduce new matter.

Additionally, Applicants respectfully submit that all the sequences in amended claims 4 and 5 correspond with the scope of the expanded examination and amended claim 1.

Claim Objections

Claim 4 was objected to for the alleged absence of the phrase "wherein the". Applicants have reviewed the claim and have amended same to correct the informality without altering the scope of the claim.

Claim 10 was objected to under 37 CFR 1.821(d) because it lacks a sequence identifier. Applicants respectfully request withdrawal of this objection in light of the amendment to claim 10.

Claim Rejections under 35 USC § 112, second paragraph

Claims 2 and 9 were rejected under 35 USC § 112, second paragraph as allegedly indefinite for reciting "from about 4 to about 12 amino acids" because "[i]t is unclear how many amino acids constitute 'about'".

Applicants respectfully, but strongly, traverse the instant rejection as failing to present a *prima facie* case of indefiniteness in light of the standard set forth at MPEP 2173.05(b). Specifically, it is well settled law that the term "about" is not indefinite *per se*. To the contrary, the term is acceptable if one skilled in the art would be apprised of the scope of the claim.

In claims 2 and 9, the skilled person would understand that the number of amino acids can only be an integer such that the term "about 4 amino acids" would not be so ambiguous as to cause confusion with respect to whether it would include 3 amino acids. In response to the allegation posed in the statement of the rejection, Applicants respectfully point out that the skilled person would certainly recognize "about 4 amino acids" to include 3 amino acids as well

as 5 amino acids because the language would be understood as not limited to only "4 amino acids". Similarly, the skilled person would certainly recognize that "about 12 amino acids" to include 11 amino acids as well as 13 amino acids because the language would be understood as not limited to only "12 amino acids".

Additionally, the lack of ambiguity with respect to the scope of "about 12 amino acids" is evinced in paragraph 16 of the Office Action mailed 21 May 2004, where the term was interpreted as encompassing a length of 14 amino acids.

Applicants thus respectfully submit that no *prima facie* case of indefiniteness has been presented, and this rejection may be properly withdrawn.

Claim Rejections under 35 USC § 112, first paragraph

Claims 1-10, 13 and 14 were rejected under 35 USC § 112, first paragraph as allegedly failing to "reasonably provide enablement for any peptide 'comprising'" the sequence recited in claim 1.

Applicants have carefully reviewed the statement of the instant rejection and respectfully traverse because no *prima facie* case of undue experimentation has been presented.

A priori, Applicants respectfully point out that the standard to be applied in establishing a *prima facie* case of non-enablement is set out in part at MPEP 2164.04, including *In re Marzocchi*[1] and the other cases cited therein. With reference to *Marzocchi*, the standard states in part that

> "A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. § 112, first paragraph, unless there is a reason to

[1] 439 F.2d 220, 169 USPQ 367 (CCPA 1971).

doubt the *objective* truth of the statements contained therein which must be relied on for enabling support." (underlining and italics added)

As the Examiner is no doubt aware, the above standard requires *objective* reasons to doubt the presumption of an enabling disclosure. Mere reliance on assertions of unpredictability are not enough. There must be objective reasons why undue experimentation is necessary to make and use the claimed invention.

Moreover, undue experimentation is not the same as the absence of experimentation. To the contrary, routine and repetitive experimentation, like that involved in the case of *In re Wands*[2], is entirely contrary to an assertion of non-enablement.

In the instant application, the disclosure, and thus claims, were enabling as originally filed for the full scope of the claims because no adequate and objective reasons have been presented to doubt the ability to make and use peptides and compositions as encompassed by the claims and described in the specification. The statement of the rejection appears to acknowledge the fact that production of peptides and compositions as encompassed by the claims can be made without undue experimentation.

The alleged basis of the rejection thus appears to be the "lack of sufficient guidance and predictability in determining which modifications would lead to the inhibition of $\alpha 3\beta 1$/TSP1 interaction". This focus is misplaced, however, because it presumes a requirement for absolute predictability as to which peptides will or will not have the functionalities as disclosed by the instant application. Applicants respectfully submit that this is not the appropriate standard because absolute predictability is not a requirement for objective enablement.

To the contrary, the standard is that of whether undue experimentation is required to make and use the claimed invention. Applicants respectfully submit that a skilled person

[2] 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988).

would be able to make a wide range of peptides, all of which comprise the sequence as recited in the claims and disclosed as the instant invention, and then identify their ability to function in the various activities disclosed in the instant application by using only routine and repetitive experimentation that is the antithesis of undue experimentation. Stated differently, a skilled person can make various peptides and compositions as encompassed by the claims and then use only routine and repetitive screening as "experimentation" to identify those that possess the functionalities as disclosed in the instant application.

The statement of the rejection attempts to support its position by asserting generalities relating to the concept of altered protein structures leading to altered functionalities. Without having to address the correctness of these generalities, Applicants respectfully submit that the assertions are irrelevant if *no undue experimentation is needed* to identify and use peptides as encompassed by the invention. Methods for such identification include those disclosed in the instant application and known to the skilled person.

The instant rejection also asserts, in relation to claim 4, that the invention does not provided a peptide the contains more than one of the sequences. Applicants again point out that whether such a peptide embodiment is specified is irrelevant in light of the *lack of objective reasons* why it would require undue experimentation to make and use such a peptide. No basis for undue levels of unpredictability or experimentation in practicing fusion or chimeric proteins comprising more than one of the recited sequences has been presented.

The assertions relating to disclosures of peptides comprising at least one, but not all, D-amino acids is similarly misplaced because, once again, no objective reasons have been provided as to why a skilled person would be unable to make, identify, and use peptides without undue experimentation. Again, and as explained above, sufficiency of enablement does **not** require absolute predictability as to the possible positions of all D-amino acids.

Last, and with respect to claims 13 and 14, the instant rejection appears to assert that "specific and detailed description ... of how to effectively use the pharmaceutical composition as claimed" is needed. Again, there are no objective reasons to doubt the statements in the instant application regarding the uses of the compositions as disclosed and claimed.

Moreover, no reasons as to undue levels of unpredictability in formulating and testing the compositions as claimed has been presented. In the absence of such reasons, the claimed compositions must be **presumed enabled**.

In light of the foregoing, Applicants respectfully submit that this rejection is misplaced and request its withdrawal.

Claims 1-10, 13 and 14 were rejected under 35 USC § 112, first paragraph as allegedly "failing to comply with the written description requirement." Applicants have carefully reviewed the statement of the instant rejection and respectfully traverse because no *prima facie* case of an inadequate written description has been presented.

As an initial matter, Applicants point out that the Final Guidelines noted in the statement of the instant rejection include the guidance that "[t]here is a strong presumption that an adequate written description of the claimed invention is present when the application is filed." (see page 1105, left column and the case law cited therein).

The statement of the rejection, however, does not appear to acknowledge this presumption and proceeds to assert an inadequate written description based on "the skilled artisan cannot envision all the contemplated amino acid sequence possibilities recited in the instant claims." Applicants respectfully submit that the rejection is thus in error both on the facts and on the law.

Contrary to the above quoted assertion from the instant rejection, there is no difficulty with "envisioning" or even writing down all the sequences encompassed by the claims. The formula is given, and with the above amendments to the claims, based upon the modification of the Restriction Requirement evinced by the scope of the claims as searched and examined, the peptides are clearly those having a definite number of sequence possibilities. These sequence possibilities are present in every peptide encompassed by the claims, and so there is no factual basis to support the instant rejection's assertion of inabilities by the skilled person.

As for the assertion based upon the "structural and functional properties of the claimed invention", Applicants respectfully point out that the very structures defined by the

formula recited in the claims are the structures which have been disclosed as having the functional properties in the instant application. Thus each of the sequence possibilities encompassed by the formula is a representative species supporting the scope of the claims. As such, Applicants were clearly in possession of the instant invention.

Applicants respectfully suggest the consideration of the following: does the instant application place the invention as claimed in the possession of a skilled artisan presented with the instant disclosure? For example, can that artisan practice the claimed invention? If so, the instant disclosure must, as a matter of logic, have provided an adequate written description of the invention. Applicants respectfully submit that no basis has been presented for why the skilled person cannot follow the instant disclosure to make and use all the peptides encompassed by the claims.

If an adequate written description is not present despite the possession by the skilled person of the claimed invention based on the instant disclosure, there would be the anomalous result of the application placing the claimed invention in the hands of the skilled artisan but not in the hands of the Applicants. This is flawed logic that has no basis in U.S. patent law.

To the extent that the instant rejection may be based upon a requirement for an ***actual*** "reduction to practice", Applicants respectfully and strongly traverse because no such requirement exists in U.S. patent law. To the contrary, it is well settled that U.S. patent law recognizes and permits **constructive reduction to practice** to support patentability.

In light of the above, the instant rejection is misplaced and should not have been made. Withdrawal of this rejection is respectfully requested.

Claim Rejections under 35 USC § 102

Claim 1 was rejected under 35 USC § 102(b) as allegedly anticipated by Prater et al.

Applicants have carefully reviewed the statement of the instant rejection and believe that the rejection has been obviated by the above amendments to claim 1 based upon the

modification of the Restriction Requirement evinced by the scope of the claims as searched and examined. Applicants expressly reserve the right to pursue the subject matter of peptides as encompassed by claim 1, as originally presented and wherein X_4 is I, in a divisional application.

Applicants respectfully submit that this rejection may be properly withdrawn.

Claims 1-2, 6-9, 13 and 14 were rejected under 35 USC § 102(b) as allegedly anticipated by Miles et al.

Applicants have carefully reviewed the statement of the instant rejection and respectfully submit that the instant rejection was misplaced with respect to claim 6 and continues to be misplaced at least with respect to claims 7-9 and 14. The instant rejection is misplaced with respect to canceled claim 6 as originally filed and pending claims 8 and 9 because Miles et al. do not teach or suggest any peptides comprising partial or full retro-inverso sequences as required by claim 6. Accordingly, Miles et al. cannot anticipate these claims.

Similarly, Miles et al. do not teach or suggest any peptide comprising at least one D-amino acid as required by claim 7. With respect to claim 14, Miles et al. do not teach or suggest any sterile composition as required by the claim. Accordingly, Miles et al. cannot anticipate claim 7 or claim 14.

As for the assertion of the instant rejection against claims 1-2 and 13, Applicants believe that the rejection has been obviated by the above amendments to claims 1 and 13 based upon the modification of the Restriction Requirement evinced by the scope of the claims as searched and examined. Applicants expressly reserve the right to pursue the subject matter of peptides as encompassed by claims 1 and 13, as originally presented and wherein X_2 is L, in a divisional application.

In light of the foregoing, Applicants respectfully submit that this rejection may be properly withdrawn.

Claims 1-2, 5-9, 13, and 14 were rejected under 35 USC § 102(b) as allegedly anticipated by WO 92/09628 (Atkin).

Applicants have carefully reviewed the statement of the instant rejection and respectfully submit that the instant rejection was misplaced at least with respect to claims 8, 9 and 14 because Atkin does not teach or suggest any retro-inverso synthetic peptides as required by claims 8 and 9 while also failing to teach or suggest any sterile composition as required by claim 14. Accordingly, Atkin cannot anticipate claims 8, 9 and 14.

As for the assertion of the instant rejection against claims 1-2, 5-7, and 13, Applicants believe that the rejection has been obviated by the above amendments to claims 1, 5 and 13 based upon the modification of the Restriction Requirement evinced by the scope of the claims as searched and examined. Additionally, and with respect to the invention based upon SEQ ID NO:54 (DVRF), now in new claims 46 and 47, Applicants point out that the scopes of claims 46 and 47 do not encompass a 6 amino acid peptide as taught by Atkin.

Specifically, Atkin does not teach or suggest SEQ ID NO:19 as encompassed by claim 47 and does not teach or suggest a peptide comprising SEQ ID NO:54 with an R_2 moiety of 2 or 3 amino acids. Support for 2 or 3 amino acids is found at least in claim 1 as originally filed because the concept of "R_2 is a peptide of 1 to 3 amino acids" evinces a small genus which necessarily includes the species of R_2 being any of 1, 2, or 3 amino acids.

In light of the foregoing, Applicants respectfully submit that this rejection may be properly withdrawn with respect to claims 1-2, 5-9, 13, and 14. Additionally, Applicants respectfully submit that this rejection is not applicable to new claims 46 and 47.

Claims 1-2, 6-9, 13 and 14 were rejected under 35 USC § 102(e) as allegedly anticipated by USP 6,020,312 (Edwards).

Applicants have carefully reviewed the statement of the instant rejection and respectfully submit that the instant rejection was misplaced at least with respect to claims 8, 9 and 14 because Edwards does not teach or suggest any retro-inverso synthetic peptides as required by claims 8 and 9 while also failing to teach or suggest any sterile composition as required by claim 14. Accordingly, Edwards cannot anticipate claims 8, 9 and 14.

As for the assertion of the instant rejection against claims 1-2, 6-7, and 13, Applicants believe that the rejection is in error because a peptide of the sequence XXSLRF (SEQ ID NO:19 in Edwards) is **not** within the scope of these claims as originally filed. A review of the claims in comparison to SEQ ID NO:19 in Edwards shows that the "SLRF" portion of the must precede the R_2 moiety of 1 to 3 amino acids as recited in claim 1. However, there is no additional amino acid following the "SLRF" sequence in Edwards. Accordingly, no *prima facie* case of anticipation is present because Edwards does not disclose all the limitations of the claims and thus cannot anticipate them.

Additionally, Applicants submit that this rejection has been obviated by the above amendments to claims 1 and 13 based upon the modification of the Restriction Requirement evinced by the scope of the claims as searched and examined. Applicants expressly reserve the right to pursue the subject matter of peptides as encompassed by claims 1 and 13, as originally presented and wherein X_2 is L, in a divisional application.

In light of the foregoing, Applicants respectfully submit that this rejection may be properly withdrawn.

Claim Rejections under 35 USC § 103(a)

Claims 6-8 were rejected under 35 USC § 103(a) as allegedly unpatentable over Prater et al. in view of USP 5,770,563 (Roberts et al.).

Applicants have carefully reviewed the statement of the instant rejection and respectfully submit that no *prima facie* case of obviousness has been presented.

As an initial matter, Applicants point out that claim 6 has been canceled. Additionally, and with respect to claim 7, Applicants point out that Prater et al. is no longer relevant to claim 1, from which claim 7 now depends. Accordingly, the instant rejection may be withdrawn with respect to claims 6 and 7.

With respect to claims 8 and 9, Applicants respectfully submit that the instant rejection 1) is not supported by an adequate motivation to combine, 2) lacks an expectation of

success, and 3) is based upon improper hindsight reconstruction. Each one of these three reasons constitutes, by itself, a failure to set forth a *prima facie* case of obviousness.

With respect to 1), the teaching of Prater et al. relied upon is **not** the three peptides synthesized and studied therein. Instead it is the disclosure of an entire *P. falciparum* protein (C.S. protein) which is being relied upon because there is no teaching or suggestion by Prater et al. (in Figure 8 or otherwise) to make and use only the portion of the C.S. protein shown in Figure 8 therein. Given no indication of relatedness between the *entire* C.S. protein and thrombospondin *peptides*, the combination of Prater et al. and the teachings of Roberts et al. is not supported by an adequate motivation to combine. The statement of the rejection fails to provide any reason why an artisan of ordinary skill would look to the *peptide related* teachings of Roberts et al. given the full sequence of the C.S. protein in Prater et al. In the absence of such a reason, where is the motivation to combine these references?

As for 2), the instant rejection fails to provide any basis for the expectation of successful substitution of all the positions of the *entire* C.S. protein with D-amino acids. Roberts et al. does not appear to provide any teachings or suggestions beyond D-amino acids in *peptides*, so where is the expectation of success in making and using a C.S. protein containing all D-amino acids?

Concerning 3), and in light of the above, the instant rejection appears to be based upon improper hindsight reconstruction of the invention based upon an impermissible use of the instant disclosure as a guide for combining otherwise disparate teachings in the field. Why else would the sequence of an *entire* C.S. protein be considered and combined with teachings of thrombospondin *peptides*? Prater et al.'s teachings regarding the similarities between their thrombospondin peptides and a portion of the C.S. protein is not applicable because the sequence of the Prater et al. peptides is not related to the Roberts et al. peptides.

In light of the foregoing, and regardless of the benefits of D-amino acid modified peptides described by Roberts et al., no *prima facie* case of obviousness is present because no proper combination of references has been presented. Accordingly, Applicants respectfully submit that this rejection may be properly withdrawn.

Conclusion

In light of the above amendments and arguments, Applicants respectfully submit that claims 1-19, 46, and 47 are in condition for allowance and respectfully urge earlier indication to this effect. Additionally, claims 20-45 may be properly rejoined and allowed as part of the passage of the instant application to issue.

If the Examiner believes a telephonic discussion would expedite prosecution of this application, he is encouraged to telephone the undersigned at the number provided below.

Respectfully submitted,

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